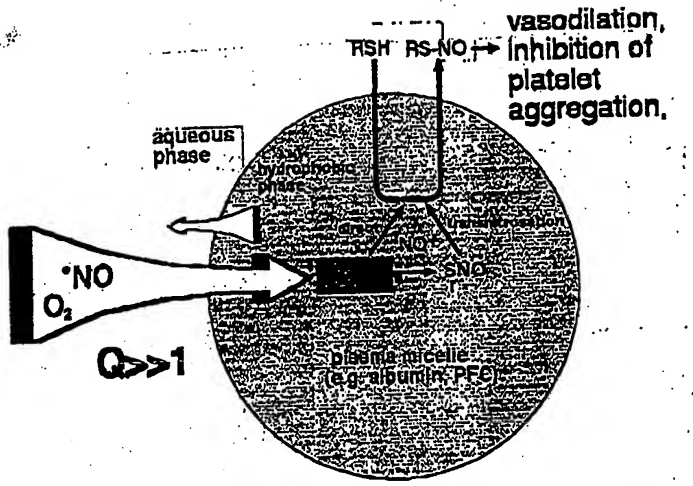


Figure 1. Micellar catalysis of NO oxidation and S-nitrosation. Hydrophobic compartments (micelles) formed by a protein globule, lipid membrane, or PFC accumulate NO and O_2 from aqueous solution thus accelerating the formation of reactive nitrosating species, N_2O_3 (NO^+-NO_2^-). N_2O_3 can react with water only at the surface of the micelle. At the same time, LMW thiols [RSH] can penetrate the micelle and be accessible for nitrosation.

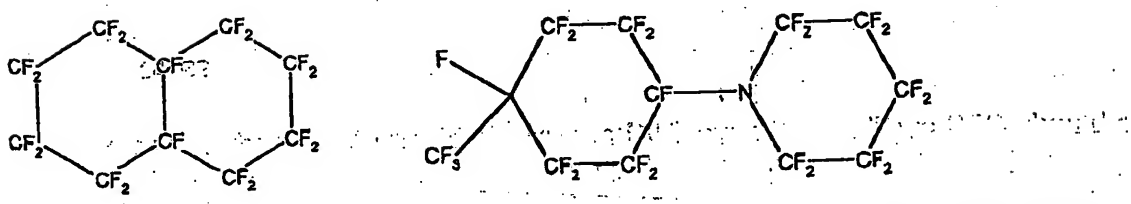


Figure 2. PFC components of Perftoran, perfluorodecaline (left) and perfluoromethylcyclopiperidine (right).

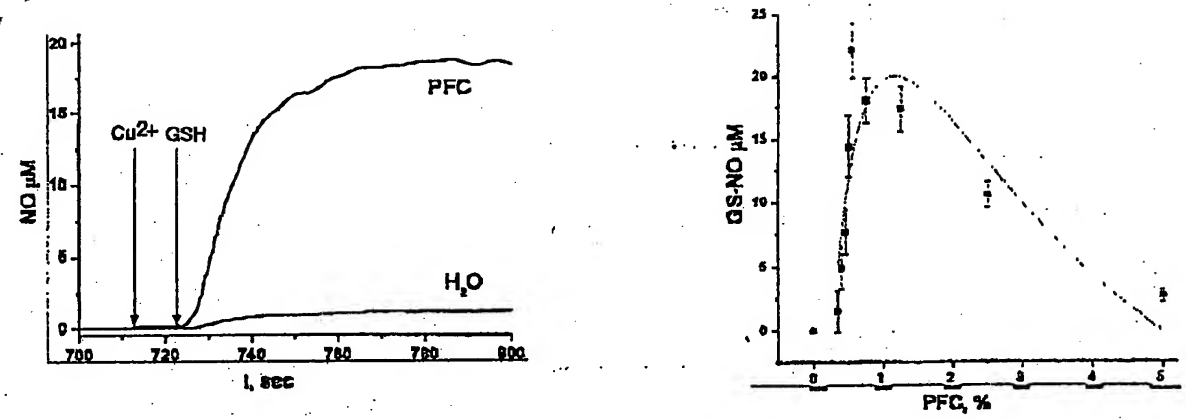


Figure 3. PFC-mediated GS-NO formation. (*Left*) A representative NO-electrode tracing of Cu^{++}-dependant NO production after an addition of GSH (1 mM) to Perftoran 1% (v/v) (PFC tracing) or control (Tris-HCl buffer [80 mM, pH 7.9]) (buffer tracing). Bolus NO (100 µM water solution) was added to Perftoran or buffer prior to GSH addition (0 sec). As soon as the concentration of NO in each probe has dropped to less than 1 µM, as detected electrochemically, GSH was added (at ~720 sec). (*Right*) PFC-mediated generation of GS-NO as a function of the volume of the hydrophobic phase (% v/v Perftoran). LMW RS-NO were determined by using $CuCl_2$ to displace NO from thiol residues followed by electrochemical detection of released NO (11).

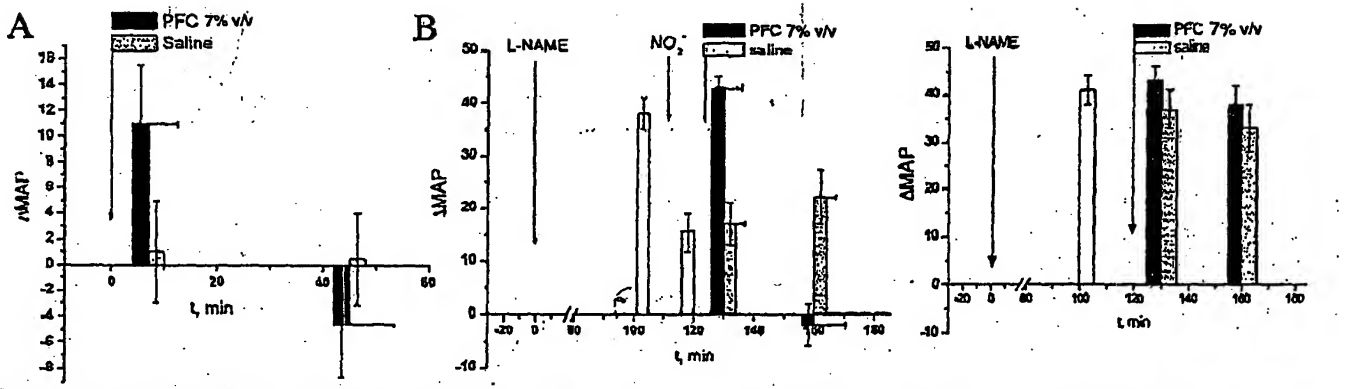


Figure 4. Control of MAP by PFC. (A) Effect of PFC (7% v/v) on MAP of anaesthetized rats. Infusion of Perftoran (5 ml/kg) produced a steep increase in blood pressure (11±4 mmHg) followed by a gradual asymptotic recovery. Delivery of Perftoran or saline iv was at a constant rate 0.2 ml/min with electronic perfusator. Mean ± SE from 11 independent experiments. (B) Relation of PFC-mediated hemodynamic effects to NO. Experiment similar to (A) except that L-NAME (50 mg/kg, 1 ml, ip) was administered (0 time point) followed by nitrite (1 mg/kg, 1ml, ip) ~1.5 hour later. After ~20 min of nitrite infusion, when arterial blood pressure had stabilized, Perftoran or saline were administered. The rightmost panel shows the control experiment without nitrite. Mean ± SE from 12 PFC experiments and 8 saline controls.

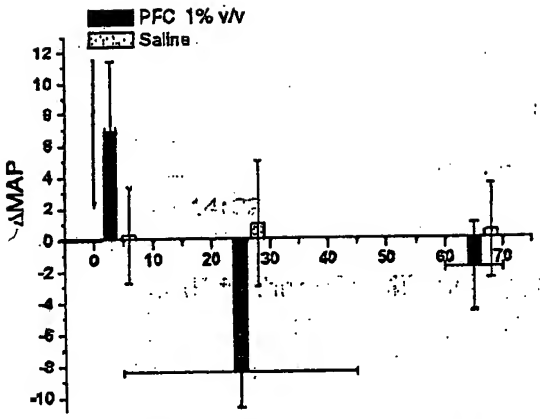


Figure 5. Effect of PFC (1% v/v) on MAP of anaesthetized rats. The experimental set up is the same as in Fig. 4A, except that the amount of administered Perftoran was 7 times less. Mean ±SE from 13 experimental animals and 9 controls.

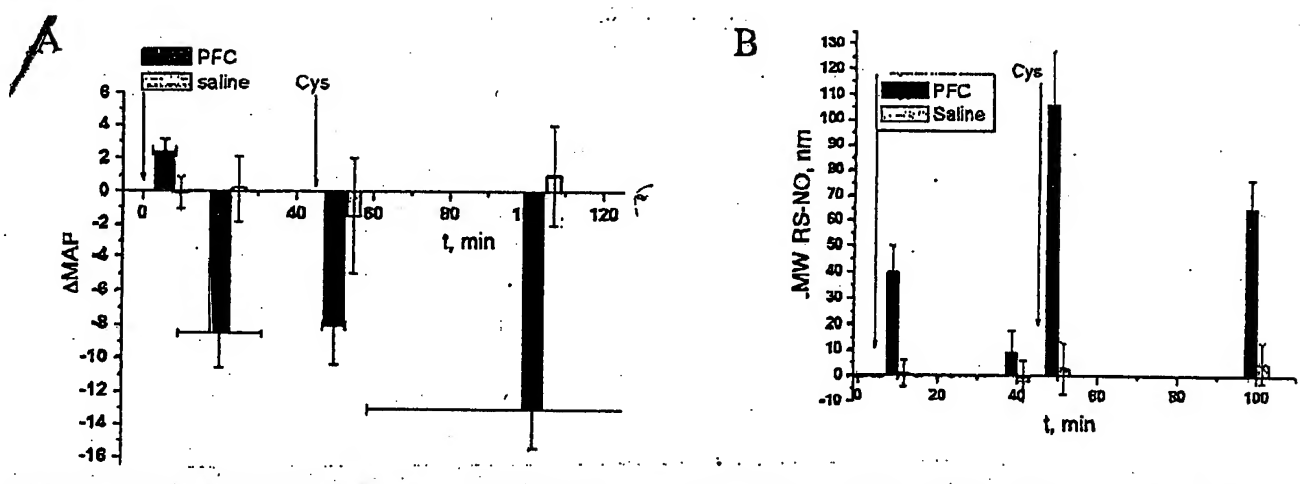


Figure 6. PFC-mediated RS-NO formation in vivo and its effect on MAP. (A) Effect of PFC (Perftoran 1% v/v, iv) +RSH (Cys, 1 mg/kg, iv) on MAP of anaesthetized rats. Experiment is similar to that of Fig. 5 except for Cys. Arrows indicate the time of PFC and Cys administration. (B) The change of plasma LMW RS-NO in response to PFC and Cys. Experimental and control animals are from (A). Arterial blood samples (0.5 ml) were collected into heparinized plastic tubes with 10 mM EDTA to prevent RS-NO decomposition. A compensatory 0.5 ml of saline was than immediately infused. Plasma LMW RS-NO were detected electrochemically as described above. Mean±SE was from 16 experimental animals and 11 controls.

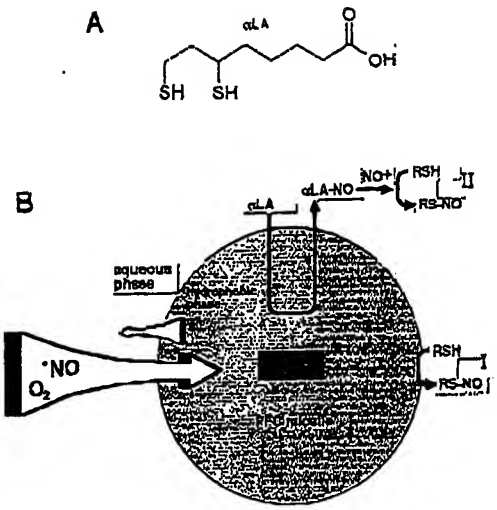
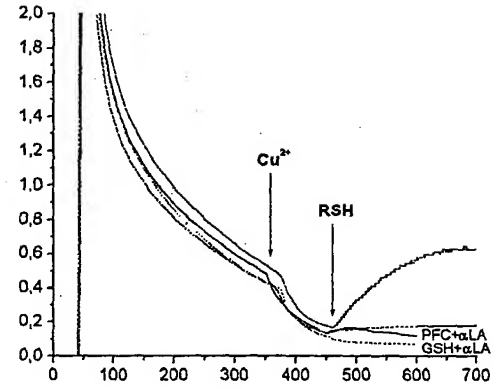


Figure 7. The proposed cascade mechanism of RS-NO formation.
A) Chemical structure of α-lipoic acid (aLA).
B) Two ways of RSH nitrosation by PFC: direct (I) and indirect via the αLA shuttle (II). αLA gets nitrosated inside the PFC micelle and transfer NO• to LMW RSH by transnitrosation.



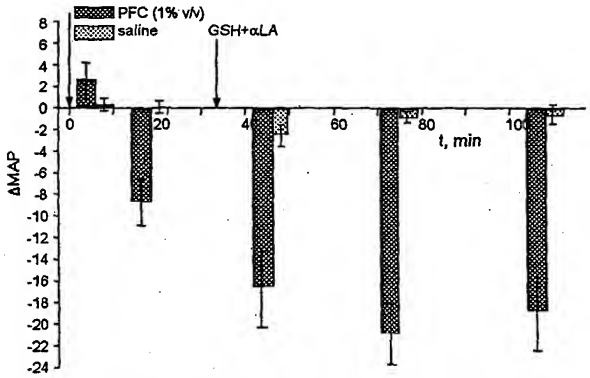
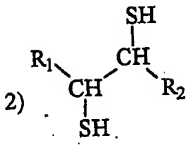
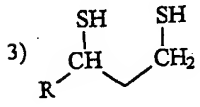


Figure 8. Stimulating effect of α-lipoic acid (αLA) on PFC-mediated GS-NO formation in vitro and vasorelaxation in rats. (A) A representative NO-electrode tracing of Cu^{++}-dependant NO production after an addition of GSH (1 mM) to Perftoran 1% (v/v) (PFC tracing) or control (Tris-HCl buffer [80 mM, pH 7.9]) (buffer tracing). Bolus NO (100 μM water solution) was added to Perftoran or buffer prior to GSH and αLA addition (0 sec). As soon as the concentration of NO in each probe has dropped to less than 1 μM, as detected electrochemically, GSH with or without αLA (10 μM) was added to 20 μM at ~450 sec. **(B)** Effect of thiols (GSH 3 mg/kg+αLA 0.6 mg/kg) and PFC (1% v/v) on MAP of anaesthetized rats. Infusion of Perftoran (5 ml/kg) produced a mild initial increase in blood pressure followed by a substantial decrease of MAP, which was significantly potentiated by thiols (compare with Figure 5). Delivery of Perftoran or saline iv was at a constant rate 0.2 ml/min with electronic perfusator. Mean ± SE from 6 independent experiments.

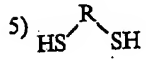
Thiols

1) R-SH (R- aromatic, alkyl, peptidil etc)
cystein, homocystein, glutathione

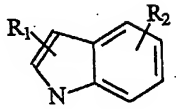
2)  1,2-dithiols

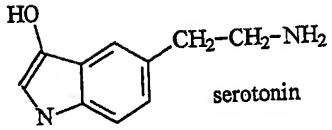
3)  1,3-dithiols (α-lipoic acid)

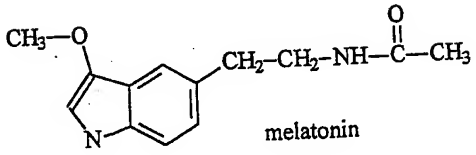
4) Three thiols?

5) 

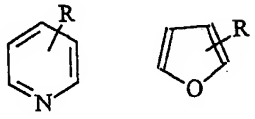
Tryptophane like




serotonin


melatonin

Piridine, heterocyclic like



Antioxidants

α - tocopherrol

FIGURE 9

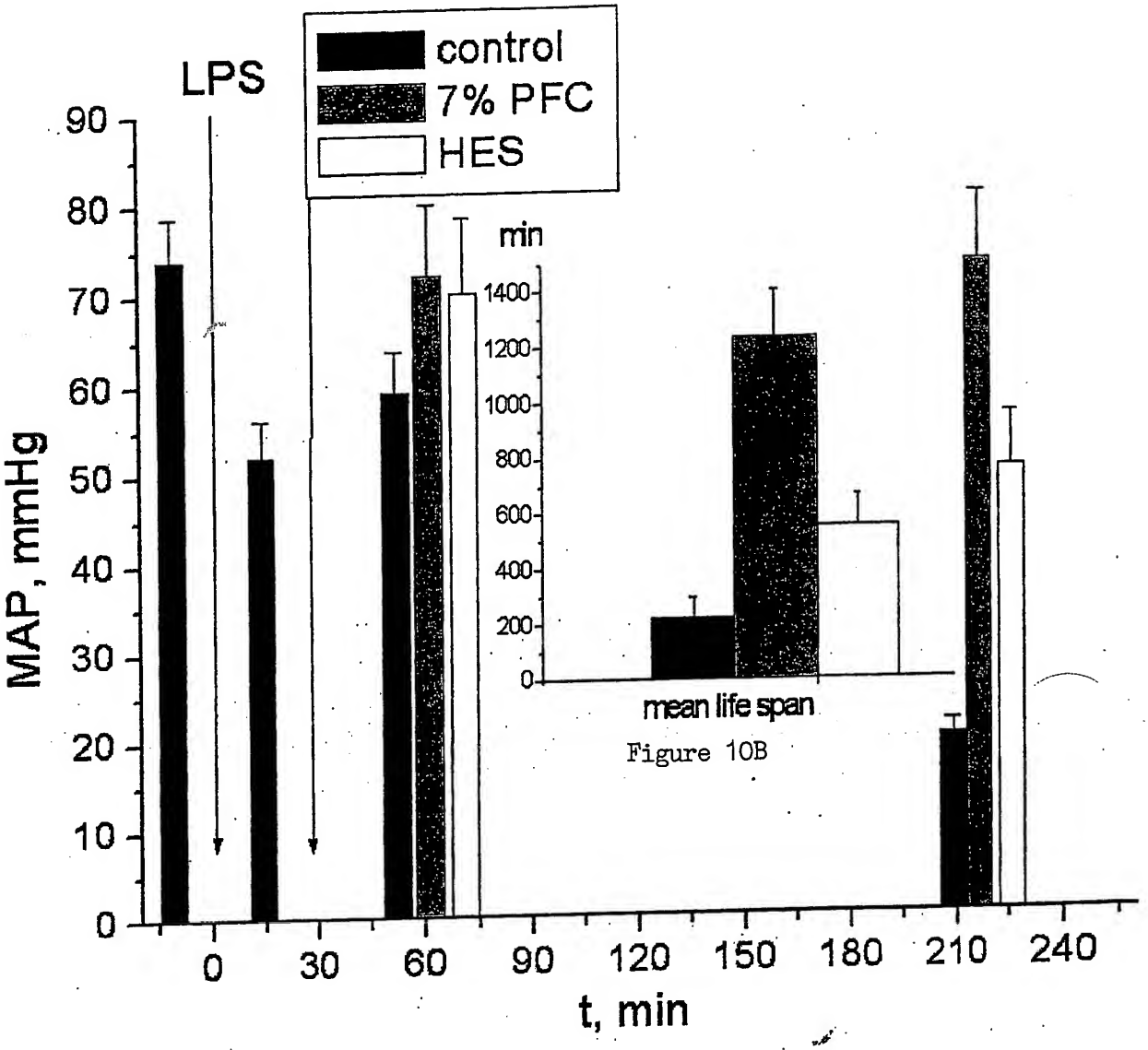


Figure 10B

Figure 10A